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Diastereoselective Hydrogenation and Kinetic Resolution of Imines Using Rhodium/Diphosphine Catalyzed Hydrogenation.

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Abstract: Kinetic resolution of racemic α -methylbenzyl amine can be achieved with 98% e.e. of the remaining amine at 70% conversion using the Rhodium/2S,4S-BDPP catalyzed asymmetric hydrogenation of imines. The same catalyst will hydrogenate optically pure α -methylbenzyl amines with a diastereoselectivity of up to 333:1.

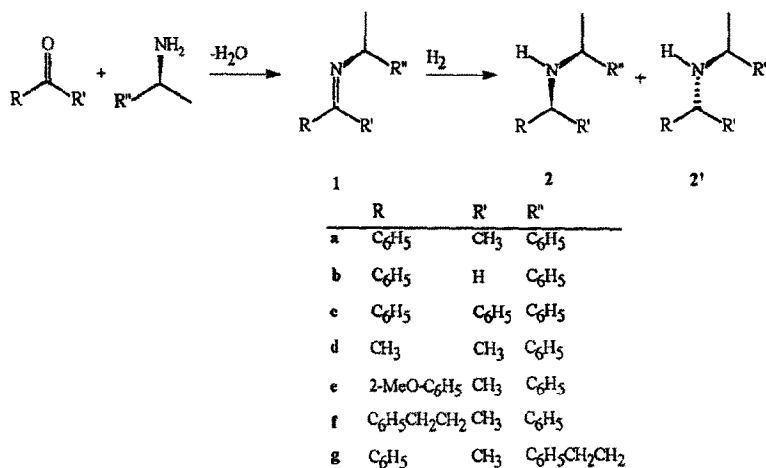
In recent years, the homogeneous hydrogenation of prochiral imines was developed by several groups.¹⁻⁴ Enantiomeric selectivities of up to 94% can now be obtained depending on the structure of the chiral diphosphine ligand used and on the structure of the imine substrate.⁵ In this paper we illustrate the use of asymmetric imine hydrogenation as a tool for the kinetic resolution of racemic α -methylbenzyl amines, and the diastereoselective synthesis of secondary amines. As the catalyst for this reaction we have used Rhodium-cyclooctadiene-chiral diphosphine complexes, usually prepared *in situ*. Homogeneous imine hydrogenation catalysts using other metals such as Iridium⁶, Ruthenium⁷ and Titanium⁸ have also been reported.

Results and discussion

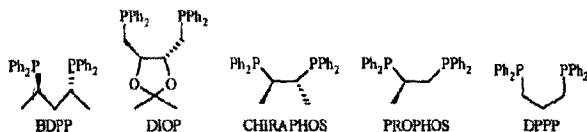
Diastereoselective hydrogenation. The reaction for the preparation of the chiral imines and the subsequent hydrogenation to secondary amines is indicated in Scheme 1. The imines are obtained in a straightforward manner by condensation of the amine with a ketone. The synthetic procedures were not optimized but pure imines could be obtained in sufficient yield to serve the purpose of our investigation. The results of the rhodium-diphosphine catalyzed hydrogenations are presented in Table 1.

The hydrogenation of **1a** using the non-chiral diphosphine ligand DPPP occurs with *threo* selectivity. Thus, R,R-bis(α -methylbenzyl) amine **2a** is formed in preference over S,R-bis(α -methylbenzyl)

Scheme 1

Table 1. The diastereoselective hydrogenation of optically pure α -methylbenzyl imines.

Imine	Ligand	product ratio RR/SR (or SS/RS)
(R)-1a	2S,4S-BDPP	333
(S)-1a	2S,4S-BDPP	15.2
(R)-1a	DPPP	10.4
(R)-1a	(-)-DIOP	13.3
(S)-1a	(-)-DIOP	12.2
(R)-1a	R-PROPHOS	1.15
(S)-1a	R-PROPHOS	2.3
(R)-1a	2S,3S-CHIRAPHOS	2.3
(S)-1a	2S,3S-CHIRAPHOS	1.5
(R)-1f	DPPP	2.0
(R)-1f	2S,4S-BDPP	5.4
(S)-1f	2S,4S-BDPP	3.2
(R)-1f	(-)-DIOP	3.9
(R)-1f	(+)-DIOP	2.2
(R)-1e	2S,4S-BDPP	51



amine **2a'** when starting from (**R**)-**1a**. This is the same selectivity as is observed for the heterogeneous hydrogenation of α -methylbenzyl imines by either Raney/Nickel or Pd/C.^{9,10} The observed diastereomeric ratio of 10.4:1 is quite respectable when compared with a selectivity of 5.7:1 obtained with Pd/C heterogeneous hydrogenation of the same substrate. The use of the chiral ligand 2S,4S-BDPP for the hydrogenation of (**R**)-**1a** gives a large increase in the diastereomeric ratio RR:SR to 333:1. Using the same ligand for the hydrogenation of (**S**)-**1a** still yields the *threo* product as the major product, but this time as the S,S-diastereomer. The product ratio SS:RS is now lowered to 15.2:1. In terms of double-stereo differentiation,¹¹ i.e. the interaction of a chiral reagent (catalyst) with a chiral substrate, we can say that the ligand 2S,4S-BDPP forms a matched pair with (**R**)-**1a** and a mismatched pair with (**S**)-**1a**. The mismatched pair, however, still results in a hydrogenation with *threo* selectivity. This is in contrast to the reversal of selectivity which is normally observed in e.g. the hydrogenation of chiral dehydriptides.¹²⁻¹⁵ Our results indicate that the selectivity of the hydrogenation of chiral imines is mainly substrate controlled. A similar observation was made for the ruthenium/BINAP catalyzed hydrogenation of allylic alcohols which is also predominantly substrate controlled.¹⁶ The other chiral diphosphine ligands we investigated are not as selective as 2S,4S-BDPP. The 2-carbon bridged ligands are not selective at all. The rate of hydrogenation decreases in the order 2S,4S-BDPP = DIOP > R-PROPHOS = CHIRAPHOS. The rates and selectivities are consistent with our earlier observations regarding the enantioselective hydrogenation of prochiral imines.¹⁷ A methoxy group in the *ortho* position of the ketone part of the imine, as in compound **1e**, reduces the selectivity to 51:1. This is still a respectable diastereoselectivity. The optically pure imines (**R**)-**1f** and (**S**)-**1f** are also hydrogenated by rhodium/2S,4S-BDPP. The same selectivity trend was observed although the diastereomeric ratio of 5.4:1 is much lower than with imine **1a**. This dependence of the selectivity of the hydrogenation on the substrate structure is again consistent with our earlier observations.¹⁷ The proximity of an aromatic ring to the C=N bond appears to be essential for a high enantioselectivity.

Kinetic resolution. The imine (**R**)-**1a** is hydrogenated at a rate which is about 10 times faster than the rate of hydrogenation of (**S**)-**1a**. The high diastereoselectivity and the rate ratio of about 10 prompted us to investigate the possible use of imine hydrogenation for the kinetic resolution of racemic amines. Because the hydrogenation of one enantiomer of the imine is faster than the hydrogenation of the other enantiomer the result will be an optical enrichment of the substrate. This is indicated in the reaction scheme below.

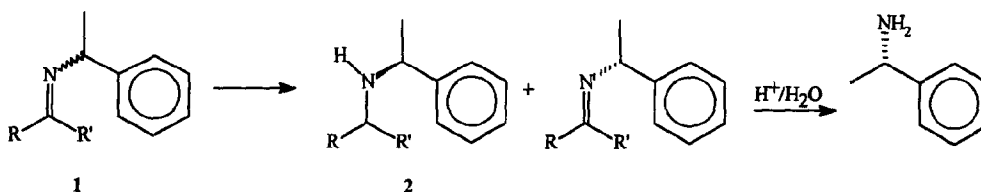


Table 2. Kinetic resolution of racemic imines.

imine	ligand	time(h)	conversion(%)	e.e.(%) of remaining imine
1a	2S,4S-BDPP	17	67	83
	(+)-DIOP	17	56	4
	2S,3S-CHIRAPHOS	145	82	7
	R-PROPHOS	17	44	2
1b	2S,4S-BDPP	2	86	19
1c	2S,4S-BDPP	17	0	
	(+)-DIOP	17	0	
	2S,3S-CHIRAPHOS	17	0	
	R-PROPHOS	17	0	
1d	2S,4S-BDPP	0.75	51	53
1e	2S,4S-BDPP	17	72	98
1g	2S,4S-BDPP	5	80	75

We analyzed the optical purity of the remaining imine by hydrolysing the imine and derivatizing the resulting primary amine with Mosher's reagent.¹⁸ The diastereomeric amides which are obtained can be analyzed by GC. With the ligand 2S,4S-BDPP the remaining imine has the expected (*vide supra*) S configuration.

The results obtained for several imines and several chiral diphosphine ligands are given in Table 2.

Consistent with our earlier observations¹⁷ and those of others,^{1,6} the 2-carbon bridged diphosphines result in catalysts which hydrogenate imines at a slow rate and with low selectivity. Only 2S,4S-BDPP results in a catalyst with a high selectivity. The rate of hydrogenation and the selectivity depends on the structure of the imine used. An imine derived from benzophenone (1d) was not hydrogenated at all whereas an imine derived from benzaldehyde (1b) was hydrogenated relatively fast but with very low selectivity. The kinetic resolution is best achieved with imines derived from acetophenone (1a) or substituted acetophenones (1e). The imine bond does not necessarily have to be prochiral. The imine derived from acetone (1d) is also hydrogenated with a reasonable selectivity.

The calculated¹⁹ rate ratio $E = k_{\text{fast}}/k_{\text{slow}} = 5.7$ at 67 % conversion for imine 1a does not correspond to the rate constant ratio $k_{\text{fast}}/k_{\text{slow}} = 10$, obtained from the measurement of the hydrogenation rates of the individual, optically pure, enantiomers of 1a. Because of this discrepancy we took a closer look at the enantiomeric excess of remaining imine as a function of conversion for the imines 1a and 1e, and compared this with the theoretically expected dependency. The results of this are presented in Figure 1. Imine 1e follows almost ideal behaviour and leads to a high enantiomeric excess in remaining substrate upon progressing of the conversion. The imine 1a on the other hand does not appear to follow ideal behaviour. The selectivity drops off at higher conversion. Not much is known about the mechanism of rhodium catalyzed imine hydrogenation. The initial binding of the imine appears to occur through the lone

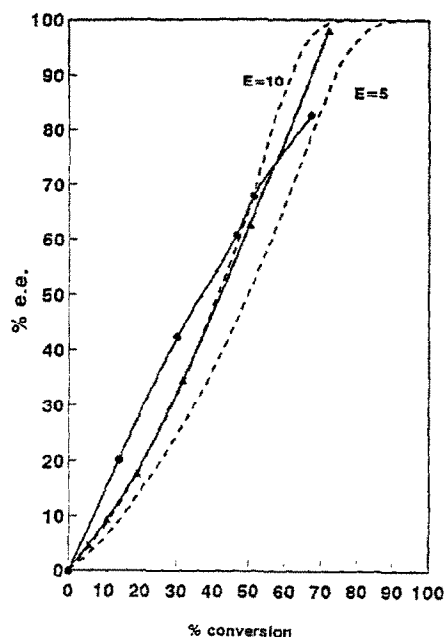


Figure 1. The kinetic resolution of 1a (+) and 1e (Δ), dashed lines are theoretical values for $E = 5$ and $E = 10$.

pair of the imine nitrogen.¹ Without knowing the mechanism of the imine hydrogenation the difference in the resolution of 1a and 1e can not be easily explained. It has been pointed out for enzymatic kinetic resolution that the determination of rate ratios using conversion and enantiomeric excess of product or remaining starting material must be treated with some caution.²⁰ When e.g. product inhibition occurs, this method of determining E is not reliable. The better resolution results obtained with 1e, i.e. a more ideal dependence of e.e. on conversion, point out that the selectivity of the imine hydrogenation can be influenced by small changes in the imine structure.

Experimental

Reagents and instrumentation. (R)-, (S)- and racemic α -methylbenzyl amine (Fluka), acetophenone (Janssen), 4-phenyl-2-butanone (Aldrich), benzophenone (Janssen), 2S,4S-BDPP (Strem), (+)- and (-)-DIOP (Fluka), 2S,3S-CHIRAPHOS (Aldrich), R-PROPHOS (Aldrich), $[\text{Rh}(\text{COD})\text{Cl}]_2$ (Aldrich) were commercial products and used as received. Solvents for the hydrogenation were degassed before use. The imines 1a-d were prepared by standard literature methods.^{10,21,22} NMR spectra were recorded on a Bruker APC2000 spectrometer in CDCl_3 .

2-(4-Phenyl-N-(2-phenylethylidene))butylamine (1g): 4-phenyl-2-aminobutane (29.4 g, 197.5

mmol) and acetophenone (24.0 g 197.5 mmol) were dissolved in toluene (150 mL) and kept on molecular sieves 4 Å (ca. 20 g) for 1 week. The imine **1g** (88.6 mmol) was isolated by vacuum distillation (b.p. 150-170 °C/ 1 mmHg), the purity checked by GC was > 98 %, *anti/syn* ratio as determined by ¹H nmr was 8.6:1. ¹H NMR (CDCl₃, 200MHz) δ 2.15 (s, N=CCH₃ (major)), 2.29 (s, N=CCH₃ (minor)), 1.18 (d, J = 6.3 Hz, N-CCH₃ (major)), 1.10 (d, 6.8 Hz, N-CCH₃ (minor)), 1.95 (m, 2H, PhCH₂CH₂), 2.60 (m, 2H, PhCH₂), 3.63 (m, 1H, N-CH), 7.1-7.8 (m, 10H, H_{arom}). ¹³C NMR (CDCl₃) δ major 15.4, 21.3, 33.0, 40.0, 54.9, 163.2; δ minor 22.2, 29.3, 39.8, 56.4.

(R)-1-Phenyl-N-2-(4-phenylbutylidene)ethylamine (1f): 4-phenyl-2-butanone (4.84 g, 32.7 mmol) and (R)-α-methylbenzyl amine (4.85 g, 40 mmol) were dissolved in toluene (50 mL). Molecular sieves 4 Å (ca. 10 g) were added. After one week the solvent was removed under reduced pressure and the product (4.82 g, 18.8 mmol) was isolated by vacuum distillation (150-160 °C/ 1 mmHg). *anti/syn* ratio as determined by ¹H nmr was 4.4:1. ¹H NMR (CDCl₃, 200MHz) δ 1.43 (d, J=6.6Hz, CHCH₃ (major)), 1.39 (d, J=6.8Hz, CHCH₃ (minor)), 1.84 (s, NCCCH₃ (major)), 2.07 (s, NCCCH₃ (minor)), 2.55-2.95 (m, CH₂CH₂), 4.60 (q, J=6.6Hz, CHCH₃ (major)), 4.12 (m, J=6.8Hz, CHCH₃ (minor)), 7.1-7.8 (m, H_{arom}). ¹³C NMR (CDCl₃) δ major 24.7, 54.0, 17.8, 44.1, 32.7, 167.4. (S)-**1f** was prepared in an identical way.

(R,R)-Bis(1-phenylethyl)amine (2a): [Rh(COD)Cl]₂ (48.8 mg, 0.099 mmol), 2S,4S-BDPP (98.8 mg, 0.22 mmol) were dissolved in methanol (20 mL) and stirred for 30 min. The imine (R)-**1a** (2.25g, 10.1 mmol) was added. The reaction solution was transferred to the autoclave under argon. The autoclave was flushed three times with H₂ and then pressurized at 1000 psi with H₂. After 17 h (R,R)-**2a** (2.15g, 9.6 mmol) was isolated by bulb-to-bulb distillation. The obtained product was only contaminated with (R,S)-**2a'** which was present in 0.3% (GC analysis). Compound **2a** can be recrystallized as its HCl salt. ¹H and ¹³C spectra were consistent with published data.¹⁹ [α]_D^{RT} +158.3 (c 3.13, EtOH).

Hydrogenation. General procedure: [Rh(COD)Cl]₂ and the appropriate amount of diphosphine were dissolved in degassed methanol in a schlenk tube under an argon atmosphere such that a solution of rhodium diphosphine complex was obtained with a concentration of 0.5·10⁻² M. After stirring this solution for 30 min. the imine substrate was added in such an amount that a imine concentration of 0.5 M was obtained. The solution was transferred via syringe to a hastelloy-C 50 mL Parr autoclave which had been flushed with argon prior to the transfer. The autoclave was flushed three time with H₂ at 1000 psi and then pressurized with H₂ to 1000 psi. The contents of the autoclave was kept under pressure and stirred at 20°C for the required time.

Analysis of the hydrogenation products. For the diastereoselective hydrogenations, the conversion and selectivity was determined by GC analysis of the crude reaction mixture. For the kinetic resolution experiments, samples were taken at regular time intervals. The conversion of the reaction was determined by GC analysis of the crude reaction mixture. The enantiomeric excess of the remaining imine was determined in the following way. Hydrolysis of the crude product with 3N HCl followed by standard acid/base workup gave a mixture of primary amine and secondary amines. The e.e. of recovered primary

amine was determined by derivatization with Mosher's reagent and GC analysis of the thus obtained mixture of diastereomeric amides.¹⁸

Conclusion

We have demonstrated that rhodium/diphosphine catalyzed asymmetric hydrogenation of imines can be used to obtain α -methylbenzyl amines in high optical yields by kinetic resolution of the corresponding racemic imines. The diastereoselective hydrogenation of optically pure imines using 2S,4S-BDPP as a ligand for the homogeneous rhodium catalyzed hydrogenation occurs with high diastereoselectivity and can be a useful tool for the preparation of a single diastereomer of secondary α -methylbenzyl amines. Initial data suggest that the approach of diastereoselective hydrogenations and kinetic resolution may result in a better understanding of the mechanism of imine hydrogenation and even the subtle ligand-substrate steric interactions responsible for the selectivity of the hydrogenation.

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